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INHALATION UPTAKE AND METABOLISM OF HALON 1301 REPLACEMENT CANDIDATES, HFC-227 ea, HFC-125, AND FC-218

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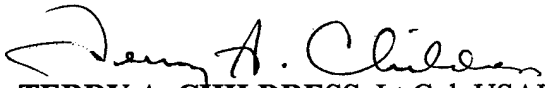

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The purpose of this study was to measure the tissue to air partition coefficients and to describe the uptake and distribution kinetics of bromotrifluoromethane's (Halon 1301) proposed replacement chemicals HFC-227ea, HFC-125, and FC-218. Parallel information pertaining to Halon 1301 and CF_3I can be found in AL/OE-TR-1994-0068.

Tissue to air partition coefficients were determined using the vial equilibration method (Gargas *et al.*, 1989). Inhalation pharmacokinetics for all Halon 1301 replacements were determined experimentally in Fischer 344 (F-344) male rats via a closed chamber recirculating gas uptake methods (Gargas *et al.*, 1986). A physiologically-based pharmacokinetic (PBPK) model was used to describe mathematically the disposition and metabolism of the chemicals employing chemical-specific parameters and apparent whole-body metabolic constants calculated from these experiments. Using these techniques, no metabolism of these chemicals were detected in Fischer 344 rats.

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PREFACE

The research reported herein was conducted by the Tri-Service Toxicology Consortium and serves as a technical report for the determination of the gas uptake pharmacokinetics of bromotrifluoromethane's (Halon 1301) proposed replacements 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea), octafluoropropane (FC-218), and pentafluoroethane (HFC-125). The research described in this report began in March 1994 and was completed in December 1994.

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ABBREVIATIONS

°C	Degrees Celsius
Halon 1301	Bromotrifluoromethane
F-344	Fischer 344 (rats)
FID	Flame ionization detector
g	Gram
GC	Gas chromatograph(y)
h	Hour
hrs	Hours
t	Time
L	Liter
m	Meter
min	Minute
mL	Milliliter
ppm	Parts per million
BW	Body weight
GI	Gastrointestinal
mm	Millimeter
CFCs	Chlorofluorocarbons
HCFCs	Hydrochlorofluorocarbons
HFCs	Hydrofluorocarbons
PBPK	Physiological Based Pharmacokinetic
CF_3I	Iodotrifluoromethane
HFC-227ea	1,1,1,2,3,3,3-Heptafluoropropane
HFC-125	Pentafluoroethane
FC-218	Octafluoropropane

SECTION 1
INTRODUCTION

Recent atmospheric measurements have indicated that the stratospheric ozone layer over the Antarctic continent may be depleted by man-made products containing chlorofluorocarbons (CFCs) and chlorofluorobromocarbons (Halons). The Montreal Protocol and global phase-out of ozone depleting CFCs and Halons has led to several proposed replacements. Many of the proposed replacements are hydrochlorofluorocarbons (HCFCs) and hydrofluorocarbons (HFCs). The HCFCs have a shorter lifetime than the ozone depleting CFCs. The HFCs only contain the halogen fluorine, which is believed not to damage the ozone layer; HFCs do not contain chlorine or bromine.

Currently the Air Force uses Halon 1301 (trifluorobromomethane), a gaseous fluorocarbon fire extinguishant agent used for unoccupied aircraft firefighting systems and in occupied total flooding areas. Halon 1301 is relatively inert and low in toxicity (Reinhart & Reinke, 1972); however, it supposedly damages the ozone layer. CF_3I (iodotrifluoromethane), HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane), HFC-125 (pentafluoroethane), and FC-218 (octafluoropropane) have been proposed as possible replacements for Halon 1301. The purpose of this study was to measure the tissue to air partition coefficients and to describe the uptake and distribution kinetics of bromotrifluoromethane's (Halon 1301) proposed replacement chemicals HFC-227ea, HFC-125, and FC-218. Parallel information pertaining to Halon 1301 and CF_3I can be found in AL/OE-TR-1994-0068.

Tissue to air partition coefficients were determined using the vial equilibration method (Gargas et al, 1989). Inhalation pharmacokinetics for all Halon 1301 replacements were determined experimentally in Fischer 344 (F-344) male rats via a closed chamber recirculating gas uptake method (Gargas et al, 1986). A physiologically based pharmacokinetic (PBPK) model was used to describe mathematically the disposition and metabolism of the chemicals employing chemical-specific parameters and apparent whole-body metabolic constants calculated from these experiments. Using these techniques, no metabolism of these chemicals were detected in Fischer 344 rats.

SECTION 2
METHODS/MATERIALS

Test Materials

1,1,1,2,3,3,3-Heptafluoropropane (HFC-227ea):

Manufacturer	Great Lakes Chemical Corp (West Lafayette, IN)
Trade Name	FM-200
CAS #	431-89-0
Mol. Weight	170 g
Empirical Formula	CF_3-CFH-CF_3
Boiling Point (^oC)	-16.4

Octafluoropropane (FC-218):

Manufacturer	3M Inc. (St Paul, Minn)
Trade Name	PF-5030 3M Performance Fluid
CAS #	76-19-7
Mol. Weight	198 g
Empirical Formula	CF_3-CF_2-CF_3
Boiling Point (^oC)	-37

Pentafluoroethane (HFC-125):

Manufacturer	DuPont Chemicals Inc. (Wilmington, DE)
Trade Name	DU002943, FE-25
CAS #	354-33-6
Mol. Weight	120 g
Empirical Formula	CHF_2-CF_3
Boiling Point (^oC)	-48.5

Animals

Male Fischer 344 (F-344) (200 to 350 g) rats (*Rattus norvegicus*) were obtained from Charles River Breeding Laboratories (Kingston, NY). Animals received Purina Formulab #5008 and softened water *ad libitum*. They were housed in plastic cages (2-3/cage) with hardwood chip bedding prior to exposure and were maintained on a 12-hr light/ 12-hr dark light cycle at constant temperature (22 +/- 1°C) and humidity (40-60%). Cages were changed twice per week. Animals were marked for identification with a tail tattoo.

The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council, DHHS. National Institute of Health Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

Partition Coefficients

Partition coefficients were determined by using a modified version of the vial-equilibration technique described by Gargas *et al.* (1989). Whole tissue was harvested and minced into a tissue slurry versus prepared as a tissue homogenate in saline. Rats used to determine partition coefficients were sacrificed with CO_2. Blood was collected from the posterior vena cava using a heparinized syringe. Liver, muscle (quadriceps), fat (epididymal and perirenal) and gastrointestinal (GI) tract (stomach and small intestine) were also removed for analysis. Partition coefficients for GI tract were not determined for FC-218. Blood samples (1.0 mL for all chemicals except for FC-218 which was 2.0 mL) were placed in 12.4 mL glass vials and incubated/ mixed for 3 hrs at 37°C with 800 ppm of chemical in the vial headspace. Whole tissue samples (1.0 g of liver and muscle, and 0.5 g of fat and GI for all chemicals except FC-218 which was 2.0 g) were minced and incubated/mixed under the same condition as for blood, except fat was equilibrated for 5-8 hrs. Partition coefficients were also determined at 80 and 400 ppm to show that they were concentration independent.

The chemical concentrations in the headspace were analyzed using a HP19395A headspace sampler (Hewlett-Packard, Avondale, PA) connected to a HP5890A gas chromatograph (GC) (Hewlett-Packard, Palo Alto, CA) equipped with a hydrogen flame ionization detector. Column selection and GC conditions varied for each chemical. For HFC-227ea, HFC-125, and FC-218 a Chromopack PoraPLOT Q (Plot Fused Silica) 25m x 0.53 mm column was used. GC conditions were set with the detector temperature at 250°C, injector temperature at 125°C, helium carrier gas at 13.0 mL/min column flow, plus 13.0 mL/min make-up flow, and an oven temperature held constant at 70°C for FC-218, 100°C for HFC-227ea, and 75°C for HFC-125.

Gas Uptake and Metabolic Constants

Figure 1 illustrates the closed chamber recirculating gas uptake system with a volume of 8.0 L that was used for the estimation of the whole animal metabolic constants (V_{maxc}, K_m, and/or K_{fc}). F-344 rats were exposed to each study chemical using a gas uptake system similar to that described by Gargas et al. (1986). Initially, a predetermined concentration of the test chemical was introduced into the system so that the concentration in the chamber atmosphere decreases as the chemical is taken up and metabolized by the rat. Four to five exposure concentrations (three rats per exposure concentration) were performed for 6 hours for each chemical (HFC-227ea concentrations were 112, 648, 1228, 2715, and 5867 ppm; HFC-125 concentrations were 132, 1005, 2725, and 5305 ppm; and FC-218 concentrations were 126, 1035, 1730, and 4825 ppm). Sodium hydroxide (75-150 g) was used as the CO_2 absorber. Oxygen concentrations were maintained at (21 +/- 1%) during the exposures. The system flow was maintained at 2.1 L/min with the flow to the sample loop of the GC at 100 mL/min.

The chemical concentrations in the chamber atmosphere were monitored every 5 min for the first 30 min and every 15 min thereafter using an automated gas sampling valve connected to a HP5890A gas chromatograph. Chromatography was performed on a 25m x 0.53 mm Chrompack PoraPLOT Q (Plot Fused Silica) column. The GC was equipped with a hydrogen flame ionization detector with a temperature of 250°C, helium carrier flow at 12.1 mL/min with

make-up flow of 14.2 mL/min, injector at 125°C, and an oven temperature held constant at 100°C for HFC-227ea, at 70°C for HFC-125, and at 70°C for FC-218.

Model Development

SIMUSOLV (DOW Chemical Co., Midland, MI), a FORTRAN-based continuous simulation language with optimization capabilities was used on a VAX/VMS 8530 mainframe computer (Digital Equipment Corp., Maynard, MA). Figure 2 shows a general form of a PBPK model with an additional compartment added to describe the gastrointestinal (GI) tract. The codes that made up the PBPK models are given in the Appendices. Parameters were optimized by SIMUSOLV which is using the log likelihood function as the criterion and either the generalized reduced gradient method for single parameter optimization or the Nelder-Mead search method for multiple parameters optimization to adjust the values.

Physiological constants for calculating volumes of the compartments are shown in Table 1. Tissue volume and flow constants are scaled to the actual body weight (BW) of the rats under study (fat volume was derived from Anderson et al. [1993]); other constants were according to Linstedt (Physiological Parameters Working Group, ILSI Risk Science Institute, unpublished data). Blood flows are expressed as a percentage of cardiac output that was scaled to body weight to the exponent 0.75. Alveolar ventilation is also scaled to body weight to the exponent 0.75. Cardiac output and alveolar ventilation, based on those described by Gargas et al. (1986) for resting animals, are summarized in Table 1.

Blood/air and tissue/air partition coefficients were obtained as described above. Metabolic constants were determined using the model to obtain a simultaneous fit to the closed chamber gas uptake data. The constants are scaled to BW using the allometric relationship described by Andersen et al. (1987).

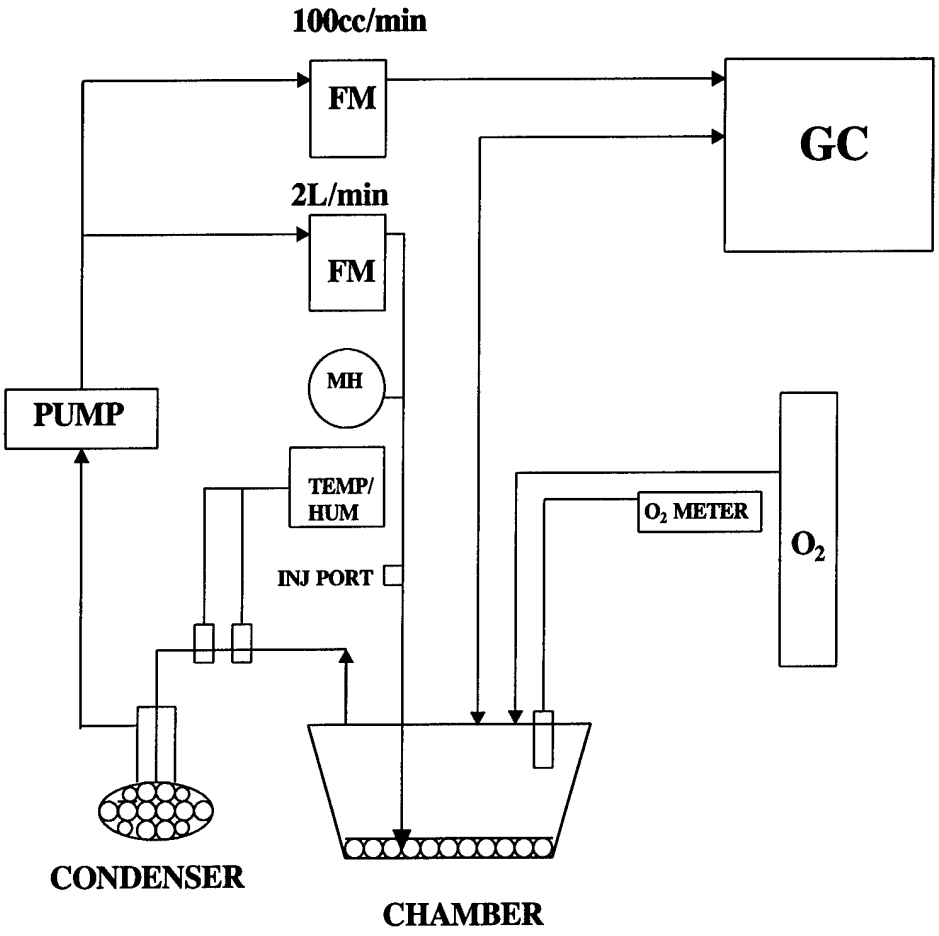


Figure 1. Illustration of Closed Chamber Recirculating Gas Uptake System (FM: flowmeter, MH: magnahelic, inj: injector, temp: temperature, hum: humidity)

TABLE 1. KINETIC CONSTANTS AND PHYSIOLOGICAL PARAMETERS USED IN PBPK MODELING IN RATS

DESCRIPTION	[UNITS] PARAMETERS
Tissue Volumes	**[Fraction of Body Weight: BW]**
Liver	$V_LC = 0.037$
Fat	$V_FC = 0.1*(35*BW+2.1)$
GI Tract	$V_GC = 0.033$
Slowly Perfused	$V_SC = 0.558$
Rapidly Perfused	$V_RC = 0.031$
Flow Rates	**[L/h/kg]**
Alveolar Ventilation	$Q_PC = 14.0$
Cardiac Output	$Q_CC = 14.0$
	[Fraction of Cardiac Output]
Liver	$Q_LC = 0.032$
Fat	$Q_FC = 0.058$
GI Tract	$Q_GC = 0.183$
Slowly Perfused	$Q_SC = 0.255$
Rapidly Perfused	$Q_RC = 0.472$

PBPK Model Construction

Figure 2 shows the scheme of the PBPK model, essentially as described by Ramsey and Andersen (1984). An additional compartment was added to describe the gastrointestinal (GI) tract. Mass transfer differential equations describing each compartment of the PBPK model for all chemicals are presented below.

For simple, well-stirred compartments in which neither metabolism nor other losses occurred (rapidly and slowly perfused tissues, fat, and gut), the change in the amount of chemical (A_i) over time (t) was described as follows:

$$dA_i/dt = Q_i(CA-CV_i)$$

where subscript $_i$ represents "i-th" compartment; Q_i represents the blood flow through the "i-th" compartment; CA represents the arterial concentration; CV_i represents the venous concentration leaving the "i-th" compartment ($CV_i = C_i/P_i$; where C_i is a concentration in the tissues in the "i-th" compartment and P_i is the tissue/ blood partition coefficient for the "i-th" compartment. $C_i = A_i/V_i$, where V_i represents the volume of the "i-th" compartment).

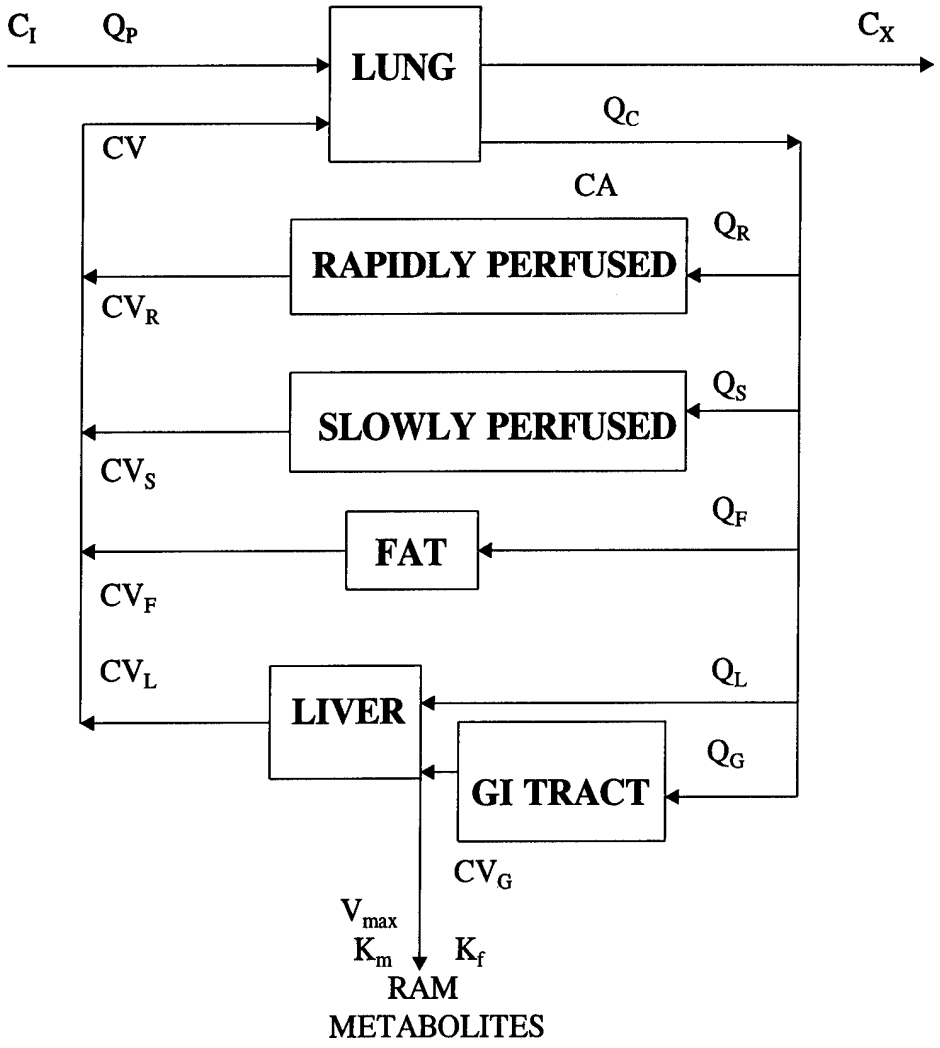


Figure 2. A Scheme of PBPK model used for the computer simulations of Halon 1301 and its proposed replacements disposition and metabolism in rats.

For the liver compartment, a loss term (RAM) was added to the well-stirred compartment description to account for rate of metabolism ($RAM = V_{max}\, CV_L/(K_m + CV_L) + K_f * CV_L * V_L$; where V_{max} is the apparent-maximal velocity rate of metabolism, CV_L is venous concentration leaving the liver, K_m is apparent Michaelis-Menten constant, K_f is the first-order rate of metabolism, and V_L is the volume of the liver):

$$dA_L/dt = Q_L(CA-CV_L)+Q_G(CV_G-CV_L)-RAM$$

where Q_G is the blood flow through the portal circulation (from the GI tract) and CV_G the concentration of the chemical that reaches the liver via portal circulation (from the GI tract). Units for the above variables are as follows: amounts-mg, concentrations-mg/L, flows-L/h, and

rates-mg/h. The actual codes and command lines used for computer simulation of Halon 1301's proposed replacements are included in the appendices.

SECTION 3
RESULTS

Partition Coefficients

Shown in Table 2 are the rat tissue to air partition coefficients determined for Halon 1301, CF_3I, HFC-227ea, HFC-125, and FC-218, which were used in the PBPK model optimization. Due to the extremely low partition coefficient for FC-218, higher amounts of rat tissue were used. Also, the addition of the GI compartment provided no additional information, and therefore for FC-218, the slowly perfused to air partition coefficients were used in the gut compartment.

TABLE 2. PARTITION COEFFICIENTS FOR HALON 1301 AND ITS PROPOSED REPLACEMENTS

Partition Coefficients		* Halon 1301 (n = 8)	* CF_3I (n = 10)	HFC-227ea (n = 4)	FC-218 (n = 10)	HFC-125 (n = 3)
Blood:air	PB	0.74 ± 0.27	1.73 ± 0.28	0.45 ± 0.19	0.25 ± 0.13	0.23 ± 0.11
Liver:air	PLA	0.81 ± 0.36	1.27 ± 0.21	0.42 ± 0.15	0.07 ±0.09	0.26 ± 0.17
Fat:air	PFA	3.6 ± 1.52	10.35± 0.82	1.58 ± 0.38	0.04 ± 0.12	0.45 ± 0.25
Gut:air	PGA	0.64 ± 0.37	1.61 ± 0.38	0.45 ± 0.2	na	0.37 ± 0.04
Rapidly perfused:air	PRA	0.81 ± 0.36	1.27 ± 0.21	0.42 ± 0.15	0.07 ± 0.09	0.26 ± 0.17
Slowly perfused:air	PSA	0.59 ± 0.21	1.32 ± 0.18	0.36 ± 0.11	0.18 ± 0.09	0.34 ± 0.29

*(Williams et al, 1994)

Gas Uptake Studies

The inhalation uptake of HFC-227ea, HFC-125, and FC-218 by the rat showed two discernible phases: a rapid equilibration phase that lasted up to 60 min followed by a slow linear uptake phase (Figures 3 through 6). HFC-227ea (Figure 3), and HFC-125 (Figure 4) were simulated without the necessity of attributing any metabolic capacity by the rats. Simulation of uptake of FC-218 required relatively high additional loss of chemical to the system. An additional first-order loss rate (K_l= 5.1) and a chamber loss of 0.8% is shown in Figure 5 to describe the simulation of uptake of FC-218 without any metabolic capacity by the rats. Figure 6 shows the simulation of uptake of FC-218 without any metabolic capacity by the rats and a chamber loss of 0.8%. The constants and rates used for each of the simulations and for the simulations of Halon 1301 and CF_3I are summarized in Table 3. The stated metabolic constants for FC-218 are used only in the simulation, and do not represent metabolic constants for FC-218 in the rat. At this time, actual distribution and uptake pharmacokinetics for FC-218 cannot be determined.

TABLE 3. SUMMARY OF METABOLIC CONSTANTS AND CHAMBER LOSS RATES USED IN SIMULATING UPTAKE OF HALON 1301 AND ITS PROPOSED REPLACEMENTS BY RATS

FIGURE	CHEMICAL	V_{maxc} mg/h/kg	K_m mg/L	K_{fc} 1/h/kg	CHAMBER LOSS / h
*	Halon 1301	0.0	10000	0.0	4.1 %
*	CF_3I	0.375	0.1	1.6	2.7 %
		0.0	10000	0.0	2.7 %
*	CF_3I	0.375	0.1	0.0	4.0 %
		0.0	10000	0.0	2.7 %
*	CF_3I	0.375	0.1	1.6	2.7 %
		0.375	0.1	0.0	4.0 %
3	HFC-227ea	0.0	10000	0.0	3.4 %
4	HFC-125	0.0	10000	0.0	3.2 %
5	# FC-218	0.0	10000	0.0	0.8 %
6	# FC-218	0.0	10000	0.0	0.8 %
					K_l=5.1%

* (Williams et al, 1994)

Stated metabolic constants are used only in the simulation, and do not represent metabolic constants for FC-218 in the rat. At this time, actual distribution and uptake pharmacokinetics for FC-218 cannot be determined.

Figure 3 - HFC-227ea Gas Uptake

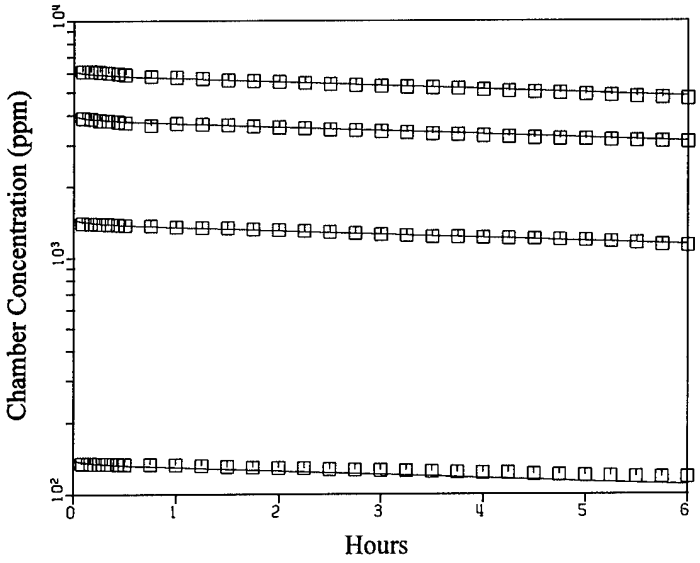


Figure 4 - HFC-125 Gas Uptake

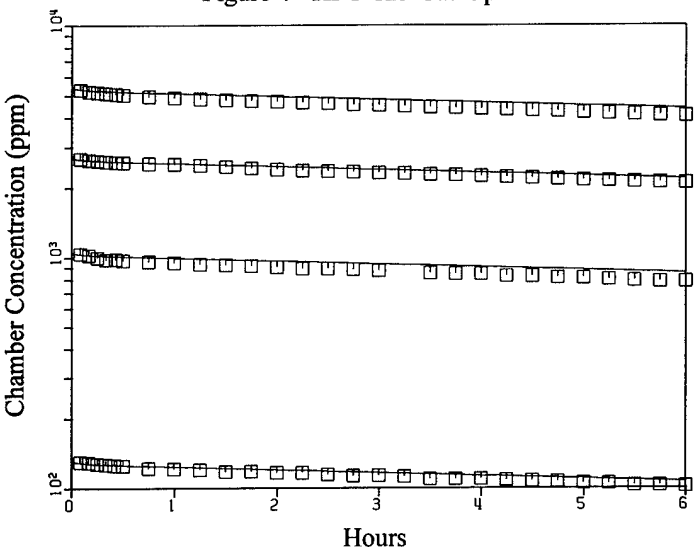


Figure 5 - FC-218 Gas Uptake (No metabolism & 5.7% loss rate)

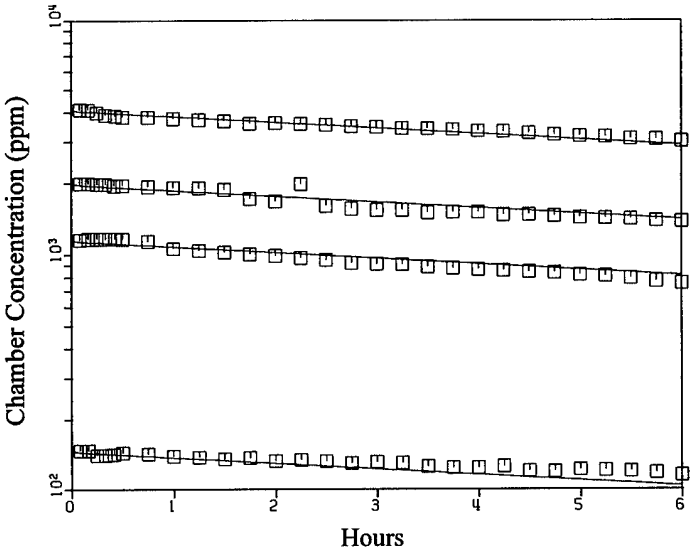
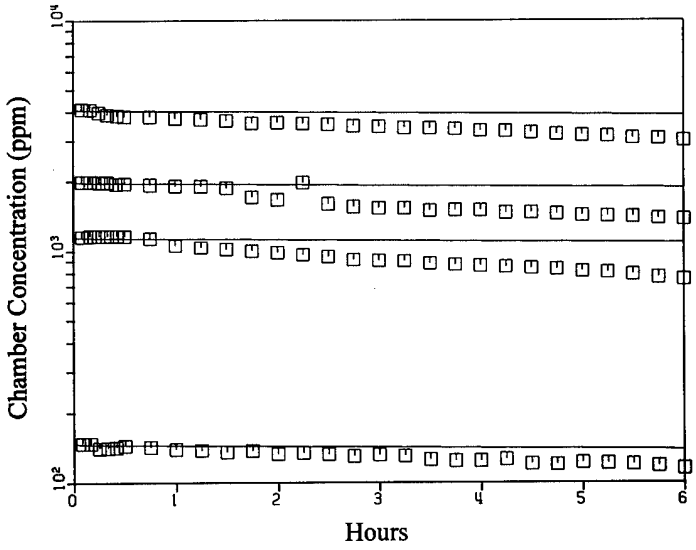


Figure 6 - FC-218 Gas Uptake (No metabolism)



SECTION 4
DISCUSSION

This simulation approach for analysis of gas uptake data has been shown to distinguish between single and multiple metabolic pathways of several previously studied dihalomethanes and numerous other volatile organic compounds. HFC-227ea, and HFC-125 gas uptake data were simulated successfully by assuming that no metabolism of the chemical was occurring and that after initial uptake by the animal further losses were those occurring in the uptake system itself.

Simulation of FC-218 required an additional first-order loss rate beyond losses to the system as determined in the loss runs. Normally, any additional loss of chemical beyond that of the system is attributed to the metabolic capacity of the rats. The inertness and the relatively low tissue to air partition coefficients of FC-218 make the possibility of first order metabolism of FC-218 seem unlikely. Loss runs were reanalyzed, and additional losses to sodium hydroxide, urine, feces, rat fur, and the system was taken into account. To further test FC-218 for possible metabolism, six rats were exposed to 10,000 ppm for 4 hours steady-state. Urine was then collected by euthanizing three rats and removing urine from the bladder, and then analyzing the urine for fluorine. Also, three rats were placed in metabolism cage and urine was collected for 12 hours and then analyzed for fluorine. The results showed no significant increase in the level of fluorine between exposed and control rats. Thus, it was determined that the presence of live rats in the system causes an additional loss of chemical that is not attributed to the metabolism of the chemical by the rats, and can not be explained by the loss runs. At this time, the actual distribution and uptake pharmacokinetics of FC-218 cannot be determined.

SECTION 5
CONCLUSION

1. The PBPK model adequately describes the uptake of HFC-227ea, and HFC-125 chemicals from the chamber atmosphere during the exposure experiments.

2. Further analysis of FC-218 determined that the PBPK model does not accurately describe the pharmacokinetics of the chemical.

3. All chemicals, HFC-227ea, HFC-125, and FC-218 have low solubility (partitioning) in blood and tissues and had minimal, if any, enzymatic metabolism in rats.

4. Further investigation is needed to describe the gas uptake distribution and pharmacokinetics for FC-218.

SECTION 6
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APPENDIX A

```
PROGRAM: CLOSED CHAMBER MODEL HFC-227ea (FM-200) GAS-UPTAKE EXPOSURES
'Based on:'
'Template Model with Code for Gut and Liver - 30 March 1993'
'_____'
INTEGER J
ARRAY CONCJ(4), BWJ(4)
CONSTANT CONCJ = 140.0,1465.0,4000.0,6160.0
CONSTANT BWJ = .242,.266,.255,.241
CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2  $'Gear method for stiff systems'

   'Timing commands'

CONSTANT   TSTOP = 6.   $'Length of experiment (hrs)'
CONSTANT    CINT = .1   $'Communication interval'

J = INT(JJ)
CONC = CONCJ(J)
BW = BWJ(J)
CONSTANT   KL  = .035   $'FIRST ORDER CHAMBER LOSS'
CONSTANT   BW = 0.23   $'Body weight (kg)'

CONSTANT   QPC = 14.00   $'Alveolar ventilation rate (l/hr)'
CONSTANT   QCC = 14.00   $'Cardiac output (l/hr)'

CONSTANT   QLC = .032  $'Fractional blood flow to liver'
CONSTANT   QGC = .183  $'Fractional blood flow to gut'
CONSTANT   QFC = .058  $'Fractional blood flow to fat'
CONSTANT   QSC = .255  $'Fractional blood flow to slow'
CONSTANT   QRC = .472  $'Fractional blood flow to rapid'

CONSTANT   VLC = .037  $'Fraction liver tissue'
CONSTANT   VGC = .033  $'Fraction gut tissue'
CONSTANT   VSC = .558  $'Fraction slow tissue'
CONSTANT   VRC = .031  $'Fraction rapid tissue'

VFC = .01*(35.0*BW+2.1)  $'Fraction fat tissue'

CONSTANT   PLA = 0.418   $'Liver/air partition coefficient'
```

```
CONSTANT  PGA = 0.445  $'Gut/air partition coefficient'
CONSTANT  PFA = 1.579  $'Fat/air partition coefficient'
CONSTANT  PSA = 0.358  $'Slowly perfused tissue/air partition'
CONSTANT  PRA = 0.418  $'Richly perfused tissue/air partition'
CONSTANT  PB =  0.454  $'Blood/air partition coefficient'

PL=PLA/PB  $'Liver/blood partition coefficient'
PG=PGA/PB  $'Gut/blood partition coefficient'
PF=PFA/PB  $'Fat/blood partition coefficient'
PS=PSA/PB  $'Slow/blood partition coefficient'
PR=PRA/PB  $'Rich/blood partition coefficient'

CONSTANT  MW = 170.0  $'Molecular weight (g/mol)'
CONSTANT  VMAXC=0. $'Maximum velocity of metabolism (mg/hr-1kg)'
CONSTANT  KM = 10000.   $'Michaelis-Menten constant (mg/l)'
CONSTANT  KFC = 0.  $'First order metabolism rate constant (/hr-1kg)'
CONSTANT  CONC=100.  $'Inhaled concentration (ppm)'
CONSTANT  RATS = 3.  $'Number of rats (for closed chamber)'
CONSTANT  VCHC = 8.0  $'Volume of closed chamber (l)'
CONSTANT  SODA = .15  $'Volume of soda lime (l)'

VCH = VCHC-(RATS*BW)-SODA  $'Net chamber volume (l)'
AI0 = CONC*VCH*MW/24450.   $'Initial amount in chamber (mg)'

   'Scaled parameters'

    QC = QCC*BW**0.75
    QP = QPC*BW**0.75
    QL = QLC*QC
    QG = QGC*QC
    QF = QFC*QC
    QS = QSC*QC
    QR = QRC*QC
    VL = VLC*BW
    VG = VGC*BW
    VF = VFC*BW
    VS = VSC*BW
    VR = VRC*BW
    VMAX = VMAXC*BW**0.75
    KF = KFC/BW**0.25
    VK = VMAXC/KM

END   $'End of initial'
```

```
DYNAMIC

DERIVATIVE

    'CI = Concentration in inhaled air (mg/l)'
    RAI = RATS*QP*(CA/PB-CI)-(KL*AI)
     AI = INTEG(RAI,AI0)                    $ 'CHAMBER'
     CI = AI/VCH                          $ 'WITH X RATS'
     CP = CI*24450./MW
'_____'
    'CA = Concentration in arterial blood (mg/l)'
     CA = (QC*CV+QP*CI)/(QC+(QP/PB))

    'AX = Amount exhaled per rat (mg)'
     CX = CA/PB
  CXPPM = (0.7*CX+0.3*CI)*24450./MW
    RAX = QP*CX
     AX = INTEG(RAX,0.)

    'AS = Amount in slowly perfused tissues per rat (mg)'
    RAS = QS*(CA-CVS)
     AS = INTEG(RAS,0.)
    CVS = AS/(VS*PS)
     CS = AS/VS

    'AR = Amount in rapidly perfused tissues per rat (mg)'
    RAR = QR*(CA-CVR)
     AR = INTEG(RAR,0.)
    CVR = AR/(VR*PR)
     CR = AR/VR

    'AF = Amount in fat tissue per rat (mg)'
    RAF = QF*(CA-CVF)
     AF = INTEG(RAF,0.)
    CVF = AF/(VF*PF)
     CF = AF/VF

    'AG = Amount in gut tissue per rat (mg)'
    RAG = QG*(CA-CVG)
     AG = INTEG(RAG,0.)
    CVG = AG/(VG*PG)
     CG = AG/VG

    'AL = Amount in liver tissue per rat (mg)'
```

```
      RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM
       AL = INTEG(RAL,0.)
      CVL = AL/(VL*PL)
       CL = AL/VL

      'AM = Amount metabolized per rat  (mg)'
      RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL  $'(mg/hr)'
       AM = INTEG(RAM,0.)                    $'Amount (mg)'

      'CV = Mixed venous blood concentration per rat (mg/l)'
       CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'
       RINH = QP*CI
       AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'
      TMASS = (AS+AR+AF+AM+AL+AX+AG)
      BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END     $'End of derivative'
END     $'End of dynamic'
END     $'End of program'
```

```
'UPTK227.CMD'
'GAS UPTAKE DATA FOR HFC-227ea'

SET TITLE = 'HFC-227ea Gas Uptake'

PREPAR T,'ALL'

SET GRDCPL=.F.    $'Turns off grid lines'

PROCED ARRAY1
SET CONCJ=140.,1465.,4000.,6160.
SET BWJ=.242,.266,.255,.241
SET J=1,JJ=1.0
END

PROCED HFC227
SET KL=.035,KFC=0.0,KM=10000.,VMAXC=0.0
SET PLA=0.418, PGA=0.445, PFA=1.579, PRA=0.418
SET PSA=0.358, PB=0.454
SET MW=170.0
SET RATS=3, VCHC=8., SODA=.15
SET QPC=14.0, QCC=14.0
DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA
END

PROCED INHAL
ARRAY1
DATA
T      CP      JJ
0.0    .       1.0  INITIAL
0.0833 134.86  .
0.1667 134.83  .
0.25   134.69  .
0.3333 134.64  .
0.4267 134.12  .
0.5    133.80  .
0.75   133.82  .
1.     133.16  .
1.25   132.02  .
1.5    130.75  .
1.75   129.90  .
2.     129.29  .
2.25   128.70  .
```

2.5 127.60 .
2.75 126.65 .
3. 126.37 .
3.25 125.62 .
3.5 125.03 .
3.75 123.84 .
4. 123.36 .
4.25 123.04 .
4.5 121.43 .
4.75 121.00 .
5. 120.06 .
5.25 119.55 .
5.5 118.63 .
5.75 118.07 .
6. 118.07 .
0.0 . 2.0 INITIAL
0.0833 1407.52 .
0.1667 1400.46 .
0.25 1397.87 .
0.3333 1392.08 .
0.4267 1384.54 .
0.5 1382.89 .
0.75 1372.20 .
1. 1354.58 .
1.25 1344.90 .
1.5 1341.54 .
1.75 1325.10 .
2. 1316.18 .
2.25 1302.17 .
2.5 1290.91 .
2.75 1276.15 .
3. 1260.97 .
3.25 1248.15 .
3.5 1231.85 .
3.75 1229.30 .
4. 1219.89 .
4.25 1214.22 .
4.5 1207.26 .
4.75 1197.14 .
5. 1189.79 .
5.25 1174.65 .
5.5 1158.31 .
5.75 1137.37 .
6. 1129.15 .

0.0	3.0	INITIAL
0.0833	3890.53	.
0.1667	3867.98	.
0.25	3816.05	.
0.3333	3796.61	.
0.4267	3759.98	.
0.5	3724.48	.
0.75	3629.25	.
1.	3699.42	.
1.25	3667.60	.
1.5	3641.95	.
1.75	3598.09	.
2.	3560.41	.
2.25	3532.68	.
2.5	3494.32	.
2.75	3462.83	.
3.	3427.72	.
3.25	3389.58	.
3.5	3348.18	.
3.75	3327.77	.
4.	3290.93	.
4.25	3261.06	.
4.5	3221.49	.
4.75	3197.29	.
5.	3178.35	.
5.25	3152.31	.
5.5	3140.64	.
5.75	3118.73	.
6.	3093.61	.
0.0	. 4.0	INITIAL
0.0833	6115.60	.
0.1667	6103.96	.
0.25	6069.83	.
0.3333	6024.79	.
0.4267	5969.95	.
0.5	5921.57	.
0.75	5817.52	.
1.	5772.08	.
1.25	5704.32	.
1.5	5612.41	.
1.75	5582.56	.
2.	5519.90	.
2.25	5466.28	.
2.5	5396.38	.

```
2.75    5356.86 .
3.      5300.86 .
3.25    5263.21 .
3.5     5228.36 .
3.75    5190.67 .
4.      5115.66 .
4.25    5053.88 .
4.5     5014.13 .
4.75    4964.25 .
5.      4899.43 .
5.25    4854.18 .
5.5     4795.68 .
5.75    4746.77 .
6.      4691.65 .
END
END
```

APPENDIX B

```
PROGRAM: CLOSED CHAMBER MODEL FC218 GAS-UPTAKE EXPOSURES
'Based on:'
'Template Model with Code for Gut and Liver - 30 March 1993'
'_____'
INTEGER J
ARRAY CONCJ(4), BWJ(4)
CONSTANT CONCJ = 147.47,1156.01,1998.59,4117.19
CONSTANT BWJ = .2707,.2336,.2137,.2185
CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2  $'Gear method for stiff systems'

   'Timing commands'

CONSTANT  TSTOP = 6.  $'Length of experiment (hrs)'
CONSTANT   CINT = .1  $'Communication interval'

J = INT(JJ)
CONC = CONCJ(J)
BW = BWJ(J)
CONSTANT  KL  = .0078  $'FIRST ORDER CHAMBER LOSS (LN AREA CTS/HR)'
CONSTANT  BW = 0.23  $'Body weight (kg)'

CONSTANT  QPC = 14.00  $'Alveolar ventilation rate (l/hr)'
CONSTANT  QCC = 14.00  $'Cardiac output (l/hr)'

CONSTANT  QLC = .032  $'Fractional blood flow to liver'
CONSTANT  QGC = .183  $'Fractional blood flow to gut'
CONSTANT  QFC = .058  $'Fractional blood flow to fat'
CONSTANT  QSC = .255  $'Fractional blood flow to slow'
CONSTANT  QRC = .472  $'Fractional blood flow to rapid'

CONSTANT  VLC = .037  $'Fraction liver tissue'
CONSTANT  VGC = .033  $'Fraction gut tissue'
CONSTANT  VSC = .558  $'Fraction slow tissue'
CONSTANT  VRC = .031  $'Fraction rapid tissue'

VFC = .01*(35.0*BW+2.1)  $'Fraction fat tissue'

CONSTANT  PLA = 0.071  $'Liver/air partition coefficient'
```

```
CONSTANT  PGA = 0.176  $'Gut/air partition coefficient'
CONSTANT  PFA = 0.043  $'Fat/air partition coefficient'
CONSTANT  PSA = 0.176  $'Slowly perfused tissue/air partition'
CONSTANT  PRA = 0.071  $'Richly perfused tissue/air partition'
CONSTANT  PB =  0.249  $'Blood/air partition coefficient'

PL=PLA/PB  $'Liver/blood partition coefficient'
PG=PGA/PB  $'Gut/blood partition coefficient'
PF=PFA/PB  $'Fat/blood partition coefficient'
PS=PSA/PB  $'Slow/blood partition coefficient'
PR=PRA/PB  $'Rich/blood partition coefficient'

CONSTANT  MW = 188.017  $'Molecular weight (g/mol)'
CONSTANT  VMAXC=0. $'Maximum velocity of metabolism (mg/hr-1kg)'
CONSTANT  KM = 10000.   $'Michaelis-Menten constant (mg/l)'
CONSTANT  KFC = 0.  $'First order metabolism rate constant (/hr-1kg)'
CONSTANT  CONC=100.  $'Inhaled concentration (ppm)'
CONSTANT  RATS = 3.  $'Number of rats (for closed chamber)'
CONSTANT  VCHC = 8.0  $'Volume of closed chamber (l)'
CONSTANT  SODA = .15  $'Volume of soda lime (l)'

VCH = VCHC-(RATS*BW)-SODA  $'Net chamber volume (l)'
AI0 = CONC*VCH*MW/24450.   $'Initial amount in chamber (mg)'

   'Scaled parameters'

    QC = QCC*BW**0.75
    QP = QPC*BW**0.75
    QL = QLC*QC
    QG = QGC*QC
    QF = QFC*QC
    QS = QSC*QC
    QR = QRC*QC
    VL = VLC*BW
    VG = VGC*BW
    VF = VFC*BW
    VS = VSC*BW
    VR = VRC*BW
    VMAX = VMAXC*BW**0.75
    KF = KFC/BW**0.25
    VK = VMAXC/KM

END   $'End of initial'
```

```
DYNAMIC

DERIVATIVE

    'CI = Concentration in inhaled air (mg/l)'
    RAI = RATS*QP*(CA/PB-CI)-(KL*AI)
     AI = INTEG(RAI,AI0)                    $ 'CHAMBER'
     CI = AI/VCH                          $ 'WITH X RATS'
     CP = CI*24450./MW
'_____'
    'CA = Concentration in arterial blood (mg/l)'
     CA = (QC*CV+QP*CI)/(QC+(QP/PB))

    'AX = Amount exhaled per rat (mg)'
     CX = CA/PB
  CXPPM = (0.7*CX+0.3*CI)*24450./MW
    RAX = QP*CX
     AX = INTEG(RAX,0.)

    'AS = Amount in slowly perfused tissues per rat (mg)'
    RAS = QS*(CA-CVS)
     AS = INTEG(RAS,0.)
    CVS = AS/(VS*PS)
     CS = AS/VS

    'AR = Amount in rapidly perfused tissues per rat (mg)'
    RAR = QR*(CA-CVR)
     AR = INTEG(RAR,0.)
    CVR = AR/(VR*PR)
     CR = AR/VR

    'AF = Amount in fat tissue per rat (mg)'
    RAF = QF*(CA-CVF)
     AF = INTEG(RAF,0.)
    CVF = AF/(VF*PF)
     CF = AF/VF

    'AG = Amount in gut tissue per rat (mg)'
    RAG = QG*(CA-CVG)
     AG = INTEG(RAG,0.)
    CVG = AG/(VG*PG)
     CG = AG/VG

    'AL = Amount in liver tissue per rat (mg)'
```

```
      RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM
       AL = INTEG(RAL,0.)
      CVL = AL/(VL*PL)
       CL = AL/VL

      'AM = Amount metabolized per rat  (mg)'
      RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL  $'(mg/hr)'
       AM = INTEG(RAM,0.)                    $'Amount (mg)'

      'CV = Mixed venous blood concentration per rat (mg/l)'
       CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'
       RINH = QP*CI
       AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'
      TMASS = (AS+AR+AF+AM+AL+AX+AG)
      BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END     $'End of derivative'
END     $'End of dynamic'
END     $'End of program'
```

```
'UPTK218.CMD'
'GAS UPTAKE DATA FOR FC-218'

SET TITLE = 'FC-218 Gas Uptake'

PREPAR T,'ALL'

SET GRDCPL=.F.    $'Turns off grid lines'

PROCED ARRAY1
SET CONCJ=147.47,1156.01,1998.59,4117.19
SET BWJ=.2707,.2336,.2317,.2185
SET J=1,JJ=1.0
END

PROCED ARRAY2
SET CONCJ=1198.6102
SET BWJ=.2474
SET J=1,JJ=1.0
END

PROCED ARRAY3
SET CONCJ=148.6143
SET BWJ=.2016
SET J=1,JJ=1.0
END

PROCED ARRAY4
SET CONCJ=5852.0608
SET BWJ=.2037
SET J=1,JJ=1.0
END

PROCED ARRAY5
SET CONCJ=5852.0608,1198.6102,147.47
SET BWJ=.2037,.2474,.2707
SET J=1,JJ=1.0
END

PROCED ARRAY6
SET CONCJ=151.42
SET BWJ=.2208
SET J=1,JJ=1.0
END
```

```
PROCED FC218
SET KL=.0078,KFC=0.0,KM=10000.,VMAXC=0.0
SET PLA=0.071, PGA=0.176, PFA=.043, PRA=0.071
SET PSA=0.176, PB=0.249
SET MW=188.017
SET RATS=3, VCHC=8., SODA=.15
SET QPC=14.0, QCC=14.0
DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA
END


PROCED INHALK
FC218
ARRAY6
DATA
T     CP     JJ
0.0    .      1.0  INITIAL
0.147  140.16 .
0.25   151.39 .
0.333  151.42 .
0.417  150.62 .
0.5    150.93 .
0.583  149.44 .
0.667  148.27 .
0.75   147.57 .
0.833  147.41 .
0.917  146.65 .
1.     146.63 .
1.083  145.22 .
1.167  145.29 .
1.25   145.51 .
1.333  143.91 .
1.417  143.76 .
1.5    143.39 .
1.583  142.78 .
1.75   141.61 .
1.833  140.60 .
1.917  140.79 .
2.0    139.78 .
2.083  139.24 .
2.167  138.77 .
2.25   138.64 .
2.333  138.59 .
```

2.417 137.77 .
2.5 137.08 .
2.583 135.95 .
2.667 136.87 .
2.75 136.06 .
2.833 134.99 .
2.917 136.15 .
3.0 134.39 .
3.083 134.23 .
3.167 134.14 .
3.25 134.05 .
3.333 133.44 .
3.417 132.3 .
3.5 132.75 .
3.583 132.14 .
3.667 132.44 .
3.75 131.89 .
3.833 131.14 .
3.917 130.66 .
4.0 131.09 .
4.083 130.79 .
4.167 130.54 .
4.25 129.94 .
4.333 128.17 .
4.417 130.03 .
4.5 129.38 .
4.583 128.98 .
4.667 128.36 .
4.75 128.25 .
4.833 127.95 .
4.917 127.52 .
5.0 127.22 .
5.083 127.43 .
5.167 126.49 .
5.25 126.40 .
5.333 125.42 .
5.417 125.39 .
5.5 122.73 .
5.583 122.31 .
5.667 121.47 .
5.75 123.2 .
5.833 121.87 .
5.917 121.84 .
6.0 119.19 .

```
END
END

PROCED INHALD
FC218
ARRAY5
DATA
T      CP      JJ
0.0    .       1.0  INITIAL
0.0833  5852.0608     .
0.1667 5769.4879      .
0.25    5731.3689     .
0.3333 5690.0924      .
0.4167 5646.0863      .
0.5     5612.2710     .
0.75    5579.4595     .
1.0     5557.8902     .
1.25    5561.5822     .
1.5     5513.1284     .
1.75    5449.7385     .
2.0     5379.6255     .
2.25    5333.4504     .
2.5     5277.8579     .
2.75    5249.1661     .
3.0     5193.1250     .
3.25    5159.1920     .
3.5     5113.1036     .
3.75    5069.3034     .
4.0     5035.0076     .
4.25    5006.8220     .
4.5     4968.9390     .
0.0    .       2.0  INITIAL
0.0833  1198.6102     .
0.1667 1184.8395      .
0.25    1176.8577     .
0.3333 1167.3379      .
0.4167 1162.4513      .
0.5     1157.8435     .
0.75    1151.9952     .
1.0     1150.4621     .
1.25    1143.2142     .
1.5     1136.1584     .
1.75    1129.9700     .
2.0     1122.1562     .
```

2.25 1117.4024 .
2.5 1107.9502 .
2.75 1103.2708 .
3.0 1098.3762 .
3.25 1089.7208 .
3.5 1083.2405 .
3.75 1072.1333 .
4.0 1054.6583 .
4.25 1044.2534 .
4.5 1040.5570 .
4.75 1038.9816 .
5.0 1035.9943 .
5.25 1031.5342 .
0.0 . 3.0 INITIAL
0.08333 147.4719 .
0.16667 147.4344 .
0.25 140.7464 .
0.33333 141.3474 .
0.41666 141.9801 .
0.5 144.1343 .
0.75 142.3753 .
1 139.4036 .
1.25 137.765 .
1.5 135.3809 .
1.75 136.9082 .
2 132.8505 .
2.25 134.3817 .
2.5 132.4036 .
2.75 129.9887 .
3 131.5743 .
3.25 130.5236 .
3.5 125.8 .
3.75 124.2447 .
4 124.2433 .
4.25 126.1631 .
4.5 120.8064 .
4.75 119.941 .
5 121.8516 .
5.25 121.2219 .
5.5 120.2678 .
5.75 118.3598 .
6 115.3991 .
END
END

```
PROCED INHALC
fc218
ARRAY4
DATA
T      CP      JJ
0.0    .       1.0  INITIAl
0.0833 5852.0608     .
0.1667 5769.4879     .
0.25   5731.3689     .
0.3333 5690.0924     .
0.4167 5646.0863     .
0.5    5612.2710     .
0.75   5579.4595     .
1.0    5557.8902     .
1.25   5561.5822     .
1.5    5513.1284     .
1.75   5449.7385     .
2.0    5379.6255     .
2.25   5333.4504     .
2.5    5277.8579     .
2.75   5249.1661     .
3.0    5193.1250     .
3.25   5159.1920     .
3.5    5113.1036     .
3.75   5069.3034     .
4.0    5035.0076     .
4.25   5006.8220     .
4.5    4968.9390     .
END
END


PROCED INHALB
fc218
ARRAY3
DATA
T      CP      JJ
0.0    .       1.0  INITIAL
0.0833 148.6143      .
0.1667 146.3137      .
0.25   .       .
0.3333 143.0546      .
0.4167 136.5264      .
```

```
0.5     136.4265     .
0.75    128.8461     .
1.0     124.9960     .
1.25    122.6735     .
1.5     121.0866     .
1.75    120.4289     .
2.0     120.4671     .
2.25    119.9398     .
2.5     119.6026     .
2.75    120.2194     .
3.0     118.9076     .
3.25    117.3958     .
3.5     115.0472     .
3.75    114.1861     .
4.0     114.2935     .
4.25    111.7556     .
4.5     110.9108     .
4.75    109.2248     .
5.0     108.1326     .
5.25    106.8036     .
5.5     106.5978     .
5.75    105.7379     .
6.0     105.5106     .
END
END


PROCED INHALA
fc218
ARRAY2
DATA
T       CP      JJ
0.0     .       1.0  INITIAL
0.0833  1198.6102    .
0.1667  1184.8395    .
0.25    1176.8577    .
0.3333  1167.3379    .
0.4167  1162.4513    .
0.5     1157.8435    .
0.75    1151.9952    .
1.0     1150.4621    .
1.25    1143.2142    .
1.5     1136.1584    .
1.75    1129.9700    .
```

2.0 1122.1562 .
2.25 1117.4024 .
2.5 1107.9502 .
2.75 1103.2708 .
3.0 1098.3762 .
3.25 1089.7208 .
3.5 1083.2405 .
3.75 1072.1333 .
4.0 1054.6583 .
4.25 1044.2534 .
4.5 1040.5570 .
4.75 1038.9816 .
5.0 1035.9943 .
5.25 1031.5342 .
END
END

PROCED INHAL
fc218
ARRAY1
DATA
T CP JJ
0.0 . 1.0 INITIAL
0.08333 147.4719 .
0.16667 147.4344 .
0.25 140.7464 .
0.33333 141.3474 .
0.41666 141.9801 .
0.5 144.1343 .
0.75 142.3753 .
1 139.4036 .
1.25 137.765 .
1.5 135.3809 .
1.75 136.9082 .
2 132.8505 .
2.25 134.3817 .
2.5 132.4036 .
2.75 129.9887 .
3 131.5743 .
3.25 130.5236 .
3.5 125.8 .
3.75 124.2447 .
4 124.2433 .
4.25 126.1631 .

4.5 120.8064 .
4.75 119.941 .
5 121.8516 .
5.25 121.2219 .
5.5 120.2678 .
5.75 118.3598 .
6 115.3991 .
0.0 . 2.0 INITIAL
0.08333 1156.0115 .
0.1667 1166.056 .
0.25 1168.5912 .
0.333 1167.2739 .
0.4267 1167.8446 .
0.5 1164.9336 .
0.75 1138.6605 .
1 1060.2355 .
1.25 1041.9862 .
1.5 1022.3474 .
1.75 1003.4074 .
2 989.0414 .
2.25 966.892 .
2.5 946.881 .
2.75 920.2177 .
3 910.73 .
3.25 905.7784 .
3.5 884.8518 .
3.75 873.8384 .
4 863.6037 .
4.25 854.8635 .
4.5 844.6226 .
4.75 834.8962 .
5 819.2434 .
5.25 810.2363 .
5.5 793.8383 .
5.75 769.8622 .
6 754.6578 .
0.0 . 3.0 INITIAL
0.08333 1998.591 .
0.1667 1996.953 .
0.25 1984.269 .
0.3333 1984.509 .
0.41667 1956.598 .
0.5 1964.067 .
0.75 1940.989 .

1 1919.335 .
1.25 1910.862 .
1.5 1883.513 .
1.75 1721.667 .
2 1679.663 .
2.25 1985.222 .
2.5 1607.976 .
2.75 1563.476 .
3 1541.913 .
3.25 1539.242 .
3.5 1503.011 .
3.75 1510.914 .
4 1508.35 .
4.25 1471.783 .
4.5 1473.536 .
4.75 1454.189 .
5 1434.735 .
5.25 1426.214 .
5.5 1413.864 .
5.75 1389.154 .
6 1381.638 .
0.0 . 4.0 INITIAL
0.08333 4117.187 .
0.1667 4112.605 .
0.25 3994.7554 .
0.333 3910.4309 .
0.4267 3863.6558 .
0.5 3836.8213 .
0.75 3828.1936 .
1 3768.5408 .
1.25 3729.8274 .
1.5 3680.865 .
1.75 3591.9463 .
2 3610.7559 .
2.25 3575.77 .
2.5 3546.0664 .
2.75 3493.2659 .
3 3466.6287 .
3.25 3422.4683 .
3.5 3411.1453 .
3.75 3387.239 .
4 3334.1572 .
4.25 3311.7539 .
4.5 3269.5215 .

```
4.75    3210.7019    .
5       3174.8623    .
5.25    3153.2417    .
5.5     3094.6743    .
5.75    3078.3196    .
6       3023.0315    .
END
END
```

APPENDIX C

```
PROGRAM: CLOSED CHAMBER MODEL HFC-125  GAS-UPTAKE EXPOSURES
'Based on:'
'Template Model with Code for Gut and Liver - 30 March 1993'
'_____'
INTEGER  J
ARRAY CONCJ(4), BWJ(4)
CONSTANT CONCJ = 131.0,1050.0,2700.0,5400.0
CONSTANT BWJ = .2305,.2201,.2161,.2388
CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2  $'Gear method for stiff systems'

    'Timing commands'

CONSTANT   TSTOP = 6.   $'Length of experiment (hrs)'
CONSTANT    CINT = .1   $'Communication interval'

J = INT(JJ)
CONC = CONCJ(J)
BW = BWJ(J)
CONSTANT   KL  = .03   $'FIRST ORDER CHAMBER LOSS'
CONSTANT   BW = 0.23   $'Body weight (kg)'

CONSTANT   QPC = 14.00   $'Alveolar ventilation rate (l/hr)'
CONSTANT   QCC = 14.00   $'Cardiac output (l/hr)'

CONSTANT   QLC = .032  $'Fractional blood flow to liver'
CONSTANT   QGC = .183  $'Fractional blood flow to gut'
CONSTANT   QFC = .058  $'Fractional blood flow to fat'
CONSTANT   QSC = .255  $'Fractional blood flow to slow'
CONSTANT   QRC = .472  $'Fractional blood flow to rapid'

CONSTANT   VLC = .037  $'Fraction liver tissue'
CONSTANT   VGC = .033  $'Fraction gut tissue'
CONSTANT   VSC = .558  $'Fraction slow tissue'
CONSTANT   VRC = .031  $'Fraction rapid tissue'

VFC = .01*(35.0*BW+2.1)  $'Fraction fat tissue'

CONSTANT   PLA = 0.264   $'Liver/air partition coefficient'
```

```
CONSTANT  PGA = 0.370  $'Gut/air partition coefficient'
CONSTANT  PFA = 0.448  $'Fat/air partition coefficient'
CONSTANT  PSA = 0.344  $'Slowly perfused tissue/air partition'
CONSTANT  PRA = 0.264  $'Richly perfused tissue/air partition'
CONSTANT  PB =  0.225  $'Blood/air partition coefficient'

PL=PLA/PB  $'Liver/blood partition coefficient'
PG=PGA/PB  $'Gut/blood partition coefficient'
PF=PFA/PB  $'Fat/blood partition coefficient'
PS=PSA/PB  $'Slow/blood partition coefficient'
PR=PRA/PB  $'Rich/blood partition coefficient'

CONSTANT  MW = 120.0  $'Molecular weight (g/mol)'
CONSTANT  VMAXC=0.0 $'Maximum velocity of metabolism (mg/hr-1kg)'
CONSTANT  KM = 10000.   $'Michaelis-Menten constant (mg/l)'
CONSTANT  KFC = 0.  $'First order metabolism rate constant (/hr-1kg)'
CONSTANT  CONC=100.  $'Inhaled concentration (ppm)'
CONSTANT  RATS = 3.  $'Number of rats (for closed chamber)'
CONSTANT  VCHC = 8.0  $'Volume of closed chamber (l)'
CONSTANT  SODA = .075  $'Volume of soda lime (l)'

VCH = VCHC-(RATS*BW)-SODA  $'Net chamber volume (l)'
AI0 = CONC*VCH*MW/24450.   $'Initial amount in chamber (mg)'

   'Scaled parameters'

    QC = QCC*BW**0.75
    QP = QPC*BW**0.75
    QL = QLC*QC
    QG = QGC*QC
    QF = QFC*QC
    QS = QSC*QC
    QR = QRC*QC
    VL = VLC*BW
    VG = VGC*BW
    VF = VFC*BW
    VS = VSC*BW
    VR = VRC*BW
    VMAX = VMAXC*BW**0.75
    KF = KFC/BW**0.25
    VK = VMAXC/KM

END   $'End of initial'
```

```
DYNAMIC

DERIVATIVE

    'CI = Concentration in inhaled air (mg/l)'
    RAI = RATS*QP*(CA/PB-CI)-(KL*AI)
     AI = INTEG(RAI,AI0)                    $ 'CHAMBER'
     CI = AI/VCH                          $ 'WITH X RATS'
     CP = CI*24450./MW
'_____'
    'CA = Concentration in arterial blood (mg/l)'
     CA = (QC*CV+QP*CI)/(QC+(QP/PB))

    'AX = Amount exhaled per rat (mg)'
     CX = CA/PB
  CXPPM = (0.7*CX+0.3*CI)*24450./MW
    RAX = QP*CX
     AX = INTEG(RAX,0.)

    'AS = Amount in slowly perfused tissues per rat (mg)'
    RAS = QS*(CA-CVS)
     AS = INTEG(RAS,0.)
    CVS = AS/(VS*PS)
     CS = AS/VS

    'AR = Amount in rapidly perfused tissues per rat (mg)'
    RAR = QR*(CA-CVR)
     AR = INTEG(RAR,0.)
    CVR = AR/(VR*PR)
     CR = AR/VR

    'AF = Amount in fat tissue per rat (mg)'
    RAF = QF*(CA-CVF)
     AF = INTEG(RAF,0.)
    CVF = AF/(VF*PF)
     CF = AF/VF

    'AG = Amount in gut tissue per rat (mg)'
    RAG = QG*(CA-CVG)
     AG = INTEG(RAG,0.)
    CVG = AG/(VG*PG)
     CG = AG/VG

    'AL = Amount in liver tissue per rat (mg)'
```

```
      RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM
       AL = INTEG(RAL,0.)
      CVL = AL/(VL*PL)
       CL = AL/VL

      'AM = Amount metabolized per rat  (mg)'
      RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL  $'(mg/hr)'
       AM = INTEG(RAM,0.)                    $'Amount (mg)'

      'CV = Mixed venous blood concentration per rat (mg/l)'
       CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'
       RINH = QP*CI
       AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'
      TMASS = (AS+AR+AF+AM+AL+AX+AG)
      BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END     $'End of derivative'
END     $'End of dynamic'
END     $'End of program'
```

```
'UPTK125.CMD'
'GAS UPTAKE DATA FOR HFC-125'

SET TITLE = 'HFC-125 Gas Uptake'

PREPAR T,'ALL'

SET GRDCPL=.F.    $'Turns off grid lines'

PROCED ARRAY1
SET CONCJ=131.0,1050.0,2700.0,5400.0
SET BWJ=.2305,.2201,.2161,.2388
SET J=1,JJ=1.0
END


PROCED HFC125
SET KL=.03,KFC=0.0,KM=10000.,VMAXC=0.0
SET PLA=.264, PGA=.370, PFA=.448, PRA=.264
SET PSA=.344, PB=.225
SET MW=120.
SET RATS=3, VCHC=8., SODA=.075
SET QPC=14.0, QCC=14.0
DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA
END

PROCED INHAL
ARRAY1
DATA
T      CP      JJ
0.0    .       1.0  INITIAL
0.08333        130.0626        .
0.16667        129.1251        .
0.25    127.5191        .
0.33333        126.7869        .
0.41667        125.7393        .
0.5     125.1457        .
0.75    121.9899        .
1.      121.2736        .
1.25    120.2045        .
1.5     117.9443        .
1.75    118.1329        .
2.      116.8297        .
2.25    116.6712        .
```

2.5 114.6224 .
2.75 113.1434 .
3. 113.5433 .
3.25 112.2831 .
3.5 109.6636 .
3.75 109.626 .
4. 109.8425 .
4.25 108.4662 .
4.5 107.9205 .
4.75 107.2097 .
5. 105.3273 .
5.25 104.8991 .
5.5 103.0726 .
5.75 102.9406 .
6. 102.1323 .
0.0 . 2.0 INITIAL
0.08333 1040.4629 .
0.1667 1024.0431 .
0.25 998.116 .
0.33333 977.4132 .
0.42667 982.3582 .
0.5 972.0569 .
0.75 959.4138 .
1. 948.9241 .
1.25 934.3019 .
1.50 928.8635 .
1.75 918.4656 .
2.00 906.3052 .
2.25 894.6522 .
2.50 894.408 .
2.75 887.0016 .
3.00 878.1715 .
3.50 856.1235 .
3.75 849.3095 .
4.00 848.9102 .
4.25 831.641 .
4.50 829.6241 .
4.75 818.9635 .
5.00 816.8447 .
5.25 804.1816 .
5.50 796.5108 .
5.75 788.8804 .
6.00 788.7296 .
0.0 . 3.0 INITIAL

0.08333 2684.372 .
0.1667 2645.462 .
0.25 2623.658 .
0.33333 2604.055 .
0.42667 2588.495 .
0.5 2578.615 .
0.75 2551.318 .
1. 2535.61 .
1.25 2505.991 .
1.50 2473.183 .
1.75 2441.515 .
2.00 2409.22 .
2.25 2386.184 .
2.50 2370.12 .
2.75 2352.056 .
3.00 2334.276 .
3.25 2319.904 .
3.50 2299.061 .
3.75 2282.594 .
4.00 2260.886 .
4.25 2237.731 .
4.50 2218.31 .
4.75 2195.022 .
5.00 2177.18 .
5.25 2162.018 .
5.50 2144.782 .
5.75 2129.483 .
6.00 2117.346 .
0.0 . 4.0 INITIAL
0.08333 5289.095 .
0.1667 5196.329 .
0.25 5148.69 .
0.33333 5109.114 .
0.42667 5072.794 .
0.5 5029.82 .
0.75 4940.921 .
1. 4885.835 .
1.25 4833.732 .
1.50 4780.267 .
1.75 4737.454 .
2.00 4704.874 .
2.25 4658.394 .
2.50 4624.226 .
2.75 4574.462 .

3.00	4537.379	.
3.25	4504.793	.
3.50	4465.162	.
3.75	4424.844	.
4.00	4389.915	.
4.25	4359.201	.
4.50	4325.972	.
4.75	4289.378	.
5.00	4244.914	.
5.25	4196.743	.
5.50	4161.696	.
5.75	4126.521	.
6.00	4102.3	.

END
END

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